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Title:

The Evans' Index revisited: New cut-off levels for use in radiological assessment of ventricular enlargement in the elderly.

Authors:

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Abstract:

Background and purpose:

Assessment of ventricular enlargement is subjective and based on the radiologist's experience. Linear indices, such as the Evans Index (EI), have been proposed as markers of ventricular volume with an EI $\geq$ 0.3 indicating pathologic ventricular enlargement in any subject. However, normal range for EI measured on magnetic resonance imaging (MRI) scans are lacking in healthy elderly according to age and sex. We propose new age and sex specific cut-off values for ventricular enlargement in the elderly population.

Materials and methods:

534 participants (53% women) aged 65-84 years; 226 patients with Alzheimer's disease (AD), and 308 healthy elderly controls (CTR) from the AddNeuroMed and ADNI studies were included. The cut-off for pathological ventricular enlargement was estimated from healthy elderly categorized into age groups of 5 years range and defined as EI 97,5 percentile (mean + 2SD). Cut-off values were tested on patients with Alzheimer's disease and a small sample of patients with probable idiopathic normal pressure hydrocephalus (iNPH) to assess the sensitivity.

Results:

The range of the EI in healthy elderly is wide and 29% of the CTR had an EI of 0.3 or greater. The EI increases with age in both CTR and AD, and the overall EI for women were lower than for men ($p<0.001$). New EI cut off values for male/female: 65-69 years 0.34/0.32, 70-74 years 0.36/0.33, 75-79 years 0.37/0.34 and 80-84 years 0.37/0.36. When applying the proposed cut-offs for EI in men and women aged 65 to 84, they differentiated between iNPH and CTR with a sensitivity of 80% and for different age and sex categories of AD and CTR with a sensitivity and specificity of 0 - 27% and 91-98%, respectively.

Conclusion:

The range of the EI measurements in healthy elderly is wide, and a cut-off value of 0.3 cannot be used to differentiate between normal and enlarged ventricles in individual cases. The proposed EI thresholds from the present study show good sensitivity for the iNPH diagnosis.

Abbreviations:

EI = Evans Index; CTR = Healthy elderly controls; AD = Alzheimer's disease; VV = Ventricular volume; ADNI = Alzheimer's disease Neuroimaging Initiative; iNPH = idiopathic normal pressure hydrocephalus

Keywords: Evans Index, Ventricular volume, Magnetic Resonance Imaging, Alzheimer's disease, idiopathic normal pressure hydrocephalus, Healthy elderly

Introduction

Tools for visual evaluation of the aging brain are published and widely used to evaluate subjects with memory impairment or other symptoms of dementia. There are scales for the evaluation of global atrophy [1] medial temporal atrophy [2] and for the classification of white matter lesions [3]. For these scales, there are also published cut-off threshold values according to age [4]. Visual inspection of the size and shape of the brain ventricles is a standard procedure in radiologic evaluation of diagnostic computer tomography (CT) and magnetic resonance imaging (MRI). Several studies have suggested that ventricular enlargement may be an objective and sensitive measure of neuropathological change associated with brain atrophy in mild cognitive impairment (MCI) and Alzheimer's disease (AD) at group level [5]. In the 2005 guidelines for diagnosis of idiopathic normal pressure hydrocephalus, an EI of 0.3 or greater combined with gait dysfunction plus either urinary or cognitive dysfunction is required prior to consideration of treatment with ventriculo-periteoneal shunt [6].

However, assessment of ventricular enlargement is in most cases performed by subjective means and is typically based on the radiologist's experience.

The Evans Index (EI) [7] is an indirect linear measurement of ventricular size initially used on pneumoencephalography in paediatric patients. In 1987, Sherman et al stated that the EI normally is smaller than 0.3 in adults and that the index can be an objective form to diagnose hydrocephalus [8]. Currently, the EI is applied as an indirect, surrogate marker of ventricular volume (VV) in CT [9] and MRI [6] in adults.

The relationship between linear indices and ratios and true VV has been evaluated in several studies using CT [10, 11] and MRI [12-14]. Two recent studies in adults have questioned the reliability of the EI for assessment of ventricular size, and volumetric analyses of VV have been suggested instead [11, 13]. Volumetric ventricular analyses are time consuming, require specialized software, and are not available in every hospital. A quick and reliable measurement of the ventricular size, to separate normal from pathologically enlarged

ventricles, is lacking in routine radiological evaluation. The EI is well known by radiologists and easy to perform, with previously reported high reliability [15].

Several studies have proposed a normal range for EI in the elderly population, but many were limited by small samples, combinations of sex and age ranges, and did not specify the method of EI measurement [10, 12, 13].

The aim of this study is to define the upper normal value of EI (97,5 percentile) in healthy elderly controls (CTR) according to sex and age. The cut off values are applied to compare EI as a marker of pathological ventricular enlargement in iNPH and AD groups, to test the method's performance for the everyday routine radiological practice. The hypotheses are: 1) the EI is not different in men and women, and 2) the EI increases with age, and differs in patients with iNPH and AD compared to healthy elderly controls (CTR).

Methods

Subjects

AD and CTR

A total of 534 participants aged 65-84 years were included; 226 patients with AD (57 % women) and 308 CTR (51 % women), see Table 1. Age did not differ between the two groups (men/women p=0.081/0.295). Data were obtained from the AddNeuroMed (33% of the participants) and the ADNI database (adni.loni.usc.edu). Participant recruitment and eligibility criteria were similar in the two cohorts [16, 17]. AddNeuroMed is part of the Innovative Medicines in Europe (InnoMed) European Union Sixth Framework program [18]. The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

Briefly, a diagnosis of AD was based on the NINCDS-ADRDA and DSM-IV criteria for probable AD, as well as a total Clinical Dementia Rating score [19] of ≥0.5. The inclusion criteria for CTR were an MMSE score of between 24 and 30, a total Clinical Dementia Rating score of 0 and a Geriatric Depression Scale score ≤5. For the CTR and AD groups, exclusion

criteria included significant neurological or psychiatric illness, significant unstable systemic illness or organ failure and history of alcohol or substance abuse or dependence.

Both the Alzheimer's disease Neuroimaging Initiative (ADNI) and the AddNeuroMed studies had ethical approval obtained from each institution involved and the data were anonymized before being shared.

iNPH

The Regional Ethics Committee (REK South-East; S-07237) and Institutional Review Board (07/5869) approved the iNPH study. Inclusion was by written and oral informed consent. 21 patients (range 56-84 years, 11 female) referred to a tertiary hospital for pre-surgical work-up of probable iNPH were included. Severity of symptoms was graded using a NPH grading scale, which assesses the combined severity of gait disturbance, urinary incontinence, and dementia [20]. Each component is graded from 1 to 5, giving a possible total score of 3 (worst) to 15 (best).

MRI Acquisition

The ADNI data was acquired at 55 sites in North America from 2004-2009, while the AddNeuroMed data was acquired at six sites across Europe from 2006-2009. The AddNeuroMed study was designed to be comparable to the ADNI study, so although data are drawn from two studies, they are homogeneous and have previously been used in other publications as combined cohorts [21]. A high-resolution sagittal 3-dimensional (3D) T1-weighted MPRAGE sequence was acquired in the AddNeuroMed and ADNI studies (voxel size1.1 x 1.1 x 1.2 mm^3). Full brain and skull coverage was required for the MRI datasets and detailed quality control was carried out on all MR images according to previously published criteria [16]. For the iNPH group, ultrafast gradient echo T1-weighted imaging was obtained with a Philips 3 T Achieva system (Philips Medical Systems, Best, The Netherlands) with sequence parameters including TR/TE = 8.6ms/2.3ms, matrix 256 x 256 x 192 and voxel size 1.0/1.0/1.0 mm^3.

The EI

The EI [7] was calculated on the individual T1-weighted axial images reconstructed from the MR images. The width was measured on three consecutive axial slices and the slice with the

largest diameter at the maximal width of the frontal horns was selected. In the same slice the largest internal diameter of the cranium (see Figure 1) was measured. If the measured maximal width of the frontal horns was identical in two or more slices, the slice with the largest internal diameter of the cranium was selected. The frontal horn diameter was divided by the largest diameter of the cranium, thus correcting for different head size in each subject. Mutually blinded operators measured the EI for AD and CTR for inter- and intra-rater reliability measurements. Indices were measured at two time points; thereafter one single operator measured all indices for all the participants.

Determination of upper normal cut-off values

EI cut-off thresholds for normal ventricular sizes were determined for each sex and 5-year age ranges in which we had a good number of subjects in each age range. The cut-off's were found by calculating the mean ± 2SD [22], which is the same as the 95% reference interval. Only the upper limit is interesting in this context as we are looking for upper normal levels of EI.

Statistical methods

Age, MMSE scores and EI between in males and females were compared between CTR and AD. Normally distributed data were analysed with either a t-test or ANOVA. When the data were not normally distributed, a log-transformation was performed, and if the data were still not normally distributed, the nonparametric Mann-Whitney U test was used. For analysis of data regarding sex, a Chi square test was used. SPSS (version 22, IBM Corp. USA) statistical analysis software package was used for all group comparison, with P-values smaller than 0.05 considered statistically significant. Neither group comparison between CTR and iNPH nor AD and iNPH were performed, as the iNPH group was small and only used to test the performance of the proposed cut-off's. Sensitivity was calculated.

In addition EI was estimated as a function of age by using non-linear regression, in particular a smoothing splines with 5 degrees of freedom and all observations as knots was used [23]. Separate estimates were determined for sex/diagnosis groups. Non-linear confidence bands were estimated at 95% level with the following procedure: First, patients were stratified into age groups including 10% of the observations each. Then, for each age group, the 2.5% and 97.5% percentiles were computed. Finally, the lower and upper bounds were respectively

estimated as a function of age by a non-linear regression of the 2.5% and 97.5% percentiles with respect to the midpoint of the age intervals, using cubic smoothing splines with the same settings. All analyses were performed in the R statistical analysis software package (v 3.1.3, 2015-03-09).

Inter- and intra-rater reliability was calculated with intraclass correlation coefficients in SPSS (version 22, IBM Corp. USA) statistical analysis software package. The operator measuring EI for the iNPH subjects were blinded to the cut off values, but not to the diagnosis.

Results

Age and sex

There were no significant age differences between the CTR and the AD group, mean age being 75 years. As expected, the MMSE scores were different between CTR and AD ($p < 0.001$), with lower values for AD versus CTR for both males and females. The EI increased with age in both CTRs and AD in males and females. This is shown in Figure 2. A general result is the broad 95% confidence bands in all groups in both males and females. A confidence band represents the uncertainty in an estimate of a curve based on limited or noisy data. Confidence bands are a good numerical approximation to the confidence intervals for the curves. The confidence bands were calculated as a smoothed bin-wise standard deviation, with at least five observations in each bin.

Upper bound cut-off values for the EI in CTR at different age ranges are made for both men and women, see Table 1. Values above the cut-off indicate enlarged ventricles.

Regarding normal reference values for healthy controls we found that the EI values in males varied between 0.22 – 0.43 and females varied between 0.19 and 0.38 for the age group 65 – 85 years. Overall there were smaller EI for women than men ($p<0.001$) for all subjects.

iNPH

Median (with range) for NPH-score was 10 (4-13).

After MRI, 17/21 patients were treated with a shunt procedure, where 16 (94 %) responded clinically defined by an improvement of at least two points at the NPH-score.

Diagnosis

In males, the mean EI was 0.29 in CTR and 0.31 in the AD group, whereas in females EI was 0.28 in CTR group and 0.29 in AD group. These group differences were significant in both males and females ($p<0.001$), see Table 1. The mean for EI in the iNPH group was (males/females) 0.37/0.37.

Sensitivity and specificity

Using the cut-off values presented in Table 2 the sensitivity and specificity of the cut-offs for separating AD and iNPH from CTR were tested. For AD, we found a sensitivity of 0 – 27 % depending on sex and age range examined, with the lowest sensitivity for males 75-79 years and females 80-84years and the highest sensitivity for females 65-69 years, and a specificity of 91 - 98%, The sensitivity for the iNPH group was 80%.

Inter-/intra-rater reliability

All reliability analyses were found to be excellent with a ICC >0.9 both for inter-rater and intra-rater analyses.

Discussion

The main finding of our study is that there is a wide range of EI in healthy elderly. Cut-off values based on healthy controls aged 65-85 shows that for age groups 65-69, 70-74, 75-79 and 80-84, the upper bound for EI was higher than 0.3 in both men and women.

The new EI cut-off values suggested here, cannot be applied to separate AD from CTR due to low sensitivity, but may separate CTR from iNPH with high sensitivity.

A recent study by Missori et al concluded that an EI > 0.3 reflects an underlying neurological condition in every individual [24]. According to our study, this would imply that 29% of all healthy elderly would wrongfully be suspected to have an underlying neurological condition. However, there is one important flaw in the statistics of the Missori paper, in which only the average EI for each age group was presented, thus ignoring the normal variation in subjects of the same age.

The EI values measured in this study are in line with results from previous MRI studies in healthy elderly subjects. If we combine the CTR female and male values from all age groups in our study, mean EI ± SD is 0.28 ± 0.03 (NO: 308, M/F: 150/158, age: 75 ± 7). Ishii et al [12] found EI to be 0.26 ± 0.003 (NO: 34, M/F: 21/13, age 75 ± 5) and Ambarki et al [13] found EI to be 0.28 ± 0.03 (NO: 46, M/F 18/28, age 71 ± 6). Nonetheless, these are not suitable as cut-off values for application in single subjects, as the merely represent averages of EI values for both sexes and any age group combined.

Several MRI studies examining the gender effects on brain structures, including VV in healthy ageing, have been published. Some studies found a different age-related regional pattern across different brain structures in men and women [25], while others found no gender differences [26]. In our study, we found that women at all ages, and in both the CTR and AD groups, have lower EI and LVV than men, and, in addition, the shape of the curves for EI are different in men and women implying that VV changes differently in males and females as we grow older. This has also been shown in a previous study of healthy elderly subjects [27]. This is in contrast to another study which showed that while men have larger brain volume, CSF volume and lateral ventricles, compared to women, VVs and intracranial areas corrected for differences in cranial size do not vary between sexes [28]. The sensitivity for detecting AD in different age groups using the cut-offs from this study was low, ranging from 0 – 21%, owing to the highly overlapping EI values between CTR and ADs. EI cut-off can therefore not be regarded as a well-suited method for diagnosing AD on MRI scans. There seems to be a smooth transition between normal and pathological values. Still it may be a valuable tool in the evaluation of brain scans from elderly patients in addition to other visual scales.

EI ≥0.3 is a suboptimal indicator when diagnosing iNPH, and diagnosing iNPH is challenging as a whole [29]. In this study, 94 % of patients treated surgically with a shunt procedure after MRI improved clinically, indicating a high proportion of what may be considered “true” iNPH. The sensitivity of detecting iNPH using the new cut off values is high (80%), and might be applied in the clinical setting. Our results need to be confirmed in larger groups of iNPH patients and unselected cases referred to the neurosurgical departments to test if the sensitivity is reproducible.

A limitation of working with databases such as AddNeuroMed and ADNI is that their population represents a clinical trial population and not an epidemiologically selected

population based study. Findings such as low educational level and increased prevalence of depression have for example been mentioned as possible confounders in the AddNeuromed study [30] and this may limit to which extent the results from this study can be generalized to the entire population. The results should be confirmed with data from other large population based cohorts.

Advantages of our study is the relatively large cohort of patients and controls compared to previous studies with EI measurements, high intra – and inter-observer reliability in the EI measurements and good clinical information about their health and cognition, which is lacking in many other studies. Cut-offs have also been tested on patients with a clinically probable iNPH diagnosis and a high shunt response rate.

In conclusion, we report normal EI ranges and propose new age-dependent cut-off values for men and women based on our healthy controls for use in routine radiological practice. EI in women are significantly lower than for men for all age intervals examined. We found that the sensitivity for discriminating AD from normal is very low in individual cases, but high in iNPH. Future studies are needed to confirm the utility of the proposed cut-off values to identify iNPH.

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Figure headings:

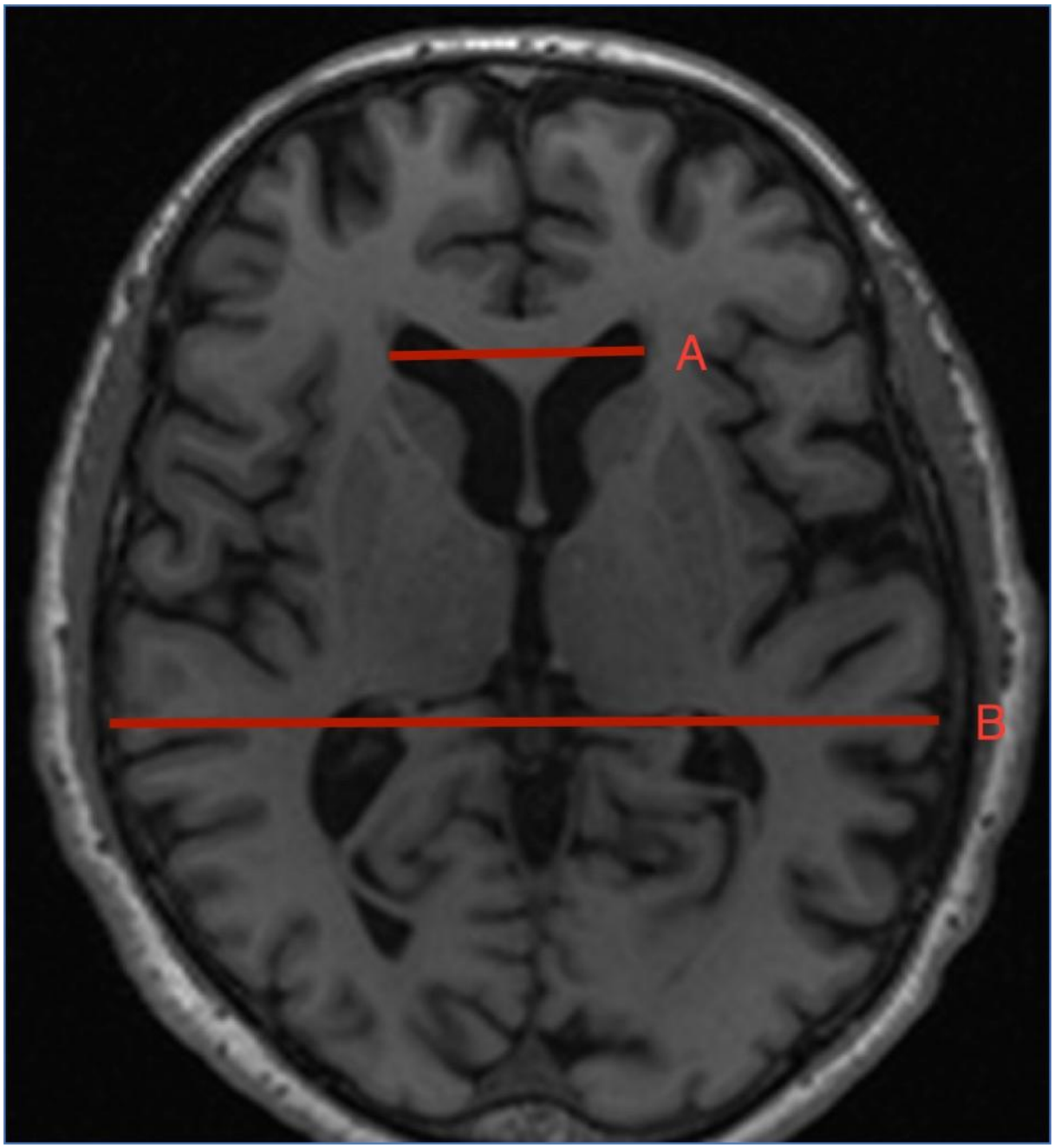

Figure 1: Evans Index. Maximal width of the frontal horns divided by the largest internal diameter of the cranium in the same slice. Evans Index = A/B

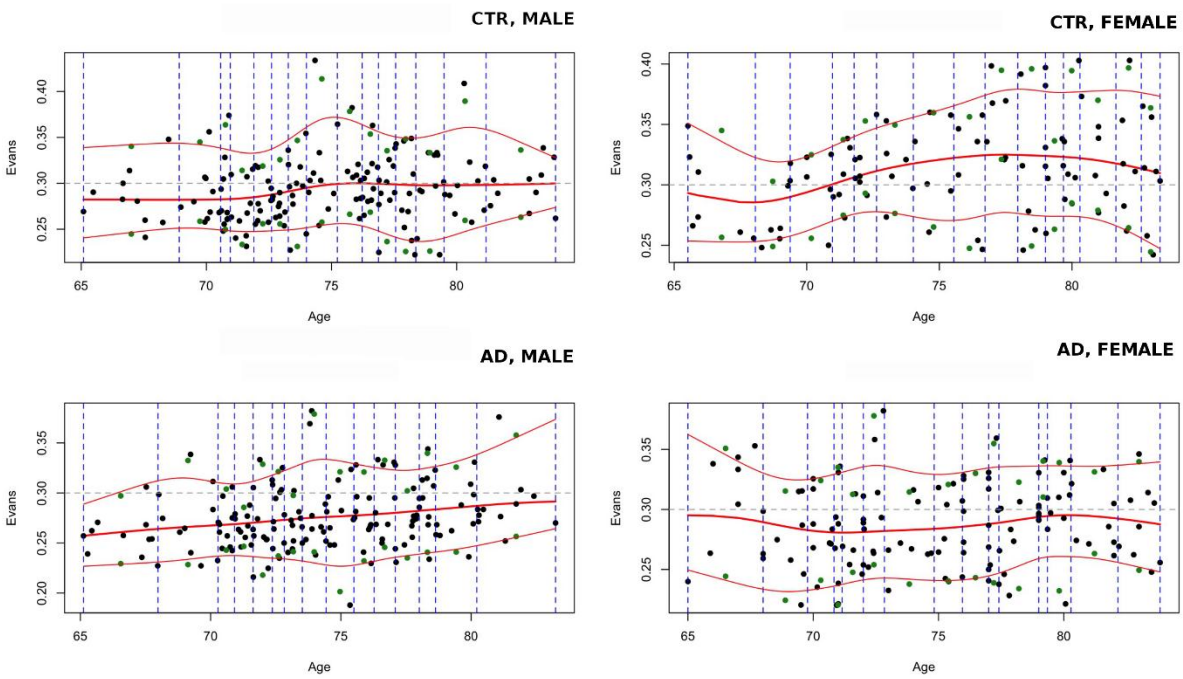

Figure 2: The non-linear relationship between EI and age for CTR and AD, men and female. The top two plots represent men and the bottom two plots represents women. The black curve in bold represents the mean value for the EI in each group, and the upper and lower black curves define the upper and lower limits of the 95% confidence bands, respectively.

Tables

Table 1: EI and other clinical data of CTR and AD

	CTR	AD	P-value
MALE			
Age, years	74.9 ± 4.2 (N=150)	75.9 ± 5.2 (N=98)	0.081
MMSE	29.0 ± 1.2 (N=150)	23.1 ± 3.1 (N=97)	< 0.001
EI	0.29 ± 0.035 (N = 150)	0.31 ± 0.039 (N = 98)	< 0.001
FEMALE			
Age, years	74.4 ± 4.2 (N=158)	75.0 ± 4.9 (N=128)	0.295
MMSE	29.2 ± 0.9 (N=156)	22.3 ± 3.7 (N=124)	< 0.001
EI	0.28 ± 0.031 (N = 158)	0.29 ± 0.034 (N=128)	0.04

Results are presented as mean ± standard deviationMMSE = Mini mental state examinationEI = Evans Index

Table 2: EI cut offs values from 308 CTR participants

Mean EI ± SD/2SD for men and women and different age range, representing the cut off values for EI.

	Male			Female		
	Mean ± 2 SD	97,5 percentile	N	Mean ± 2 SD	97,5 percentile	N
65 – 69 years	0.28 ± 0.06	0.34	11	0.27 ± 0.05	0.32	17
70 – 74 years	0.29 ± 0.07	0.36	63	0.27 ± 0.06	0.33	67
75 – 79 years	0.30 ± 0.07	0.37	55	0.28 ± 0.06	0.34	54
80 – 84 years	0.30 ± 0.07	0.37	21	0.29 ± 0.07	0.36	20
65 – 84 years	0.29 ± 0.07	0.36	150	0.27 ± 0.06	0.33	158